Branch retinal vein occlusions: a review

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ABSTRACT

Introduction: Branch Retinal Vein Occlusion (BRVO) is the second most common retinal vascular disease with a prevalence of 0.8%. The Branch Vein Occlusion Study was the first trial to show efficacy of treatment of macular oedema in BRVO with grid laser which was considered the gold standard for several years. Since then several other studies have been done on various classes of drugs and surgery and there are great strides that have been made in enhancing the visual and anatomical outcome. In this review article, we did a pubmed search of publications done over the years on the natural history of BRVO as well as the treatment options. The studies included clinical trials, systematic reviews and case reports.

Results: Currently anti-Vascular Endothelial Growth Factors (AntiVEGFs) appear to have the best outcomes in terms of anatomical and visual recovery. Other therapies that have shown promise are the intravitreal steroids, grid laser, antiVEGFs and steroids combined with lasers. Parsplana vitrectomy appears to be as efficacious as antiVEGF but is very invasive and no good clinical trials have been done yet.

Conclusion: Great strides have been made in improving the outcome of BRVO especially the macular oedema if prompt and correct treatment is administered to the patient.

Key words: Branch retinal vein occlusion, Macular oedema, Laser, Steroids, AntiVEGFS

INTRODUCTION

Retinal vascular occlusions are the second most common cause of retinal vascular disease after diabetic retinopathy[1]. Visual loss in Branch Retinal Vein Occlusion (BRVO) is due to Macular Oedema (ME), vitreous haemorrhage, capillary non-perfusion at the macula and neovascular glaucoma[2].

In this review we shall look at the natural history of the disease, the management of ME with laser, intravitreal steroids and intravitreal anti-Vascular Endothelial Growth Factor (Anti-VEGF) therapies. We shall also look at the role of sector laser photocoagulation for the resultant neovascularization that occurs in ischaemic BRVOs as well as some of the systemic therapies.

Risk factors: The pathogenesis of Retinal Vascular Occlusion (RVO) is multifactorial. BRVO may be due to a combination of three primary mechanisms: compression of the vein at the arteriovenous (A/V) crossing, degenerative changes of the vessel wall, and abnormal haematological factors[3].

Arteriorvenous (A/V) crossings: Anatomic features of A/V crossings and secondary effects of arteriolar sclerosis may explain the vulnerability of the crossing site to venous occlusion. In the majority of A/V crossings, the thin-walled vein lies between the more rigid thick-walled artery and the highly cellular retina. The artery and vein also share common adventitial sheath and the narrowing of the venous lumen that normally occurs at the A/V crossing provide the setting for BRVO[3].

Degenerative changes of vessel wall: In the area of the A/V crossing, alteration of the endothelium and intima media is present and following the compression from the overlaying artery BRVO results. The formation of the thrombus follows as a secondary process.

Systemic hypertension, diabetes mellitus, atherosclerosis, and smoking are reported to be more common in patients with RVO[3].

Haematological disorders: Haematological factors that may result in retinal vascular occlusion include hyperviscosity due to high haematocrit and dysregulation of the thrombosis-fibrinolysis balance as is seen in resistance to Activated Protein C and deficiency of Protein C or Protein S[3].

Anti-phospholipid antibodies and hyperhomocysteinemia: Circulating Antiphospholipid Antibodies (APA) leads to a hypercoagulable state and recurrent thrombosis through thrombocyte activation and inhibition of the natural anticoagulant pathways by binding of membrane phospholipids. They are associated with a 3- to 10-fold increased risk of venous thrombosis.

An elevated level of the amino acid, homocysteine is now generally accepted to be a risk factor for systemic vascular disease. Homocysteine appears to have a deleterious effect on vascular endothelium and may induce increased platelet aggregation and thrombosis[3]. The results of meta-analyses confirm total homocysteine to be an independent risk factor for RVO[4].

Natural history

Rogers *et al*[5] concluded that Visual Acuity (VA) generally improved in eyes with BRVO without intervention, although clinically significant improvement beyond 20/40 was uncommon.

Hayreh[6] noted that VA was only affected if the BRVO occurred in one of the temporal arcades. Initially in temporal BRVO, VA was 20/60 or better in 51% and 20/70 or worse in 49%. Overall, in eyes with initial VA of 20/60 or better, 75% had improved or stable VA, and in eyes with initial VA of 20/70 or worse 69% had improved VA. The median time to macular edema resolution was 21 months in major BRVO and 18 months in macular BRVO.

In a study by Hayreh and Zimmerman[7], it was established that there were 2 clear different entities. These were the major BRVO and the macular BRVO. They had different clinical presentations, progression and prognosis. Major BRVO is due to occlusion of 1 of the 4 major branch retinal veins. It involves the entire segment of the retina drained by the vein, extending all the way up to the peripheral retina. Macular BRVO is due to occlusion of one of the veins from the macular region.

The common findings established for branch retinal vein occlusions were retinal haemorrhages in the macula region, macular oedema, serous macular detachment, epiretinal membranes, serous retinal detachment, perivenous sheathing, optic disc pallor, lipid deposits, cotton wool spots, preretinal and subhyaloid haemorrhages, vascular changes which included retinal venous engorgement and attenuation in some cases, retinal arteriole attenuation and sheathing, retinal collateral. Retinal and disk neovascularization was seen only in major BRVO. The median time to resolution of major BRVO was 4 years (IQR, 2.2–9.8 years) and was 1.5 years (IQR, 1.0–6.0 years) for macular BRVO. This difference was statistically significant (P = 0.0002)[7].

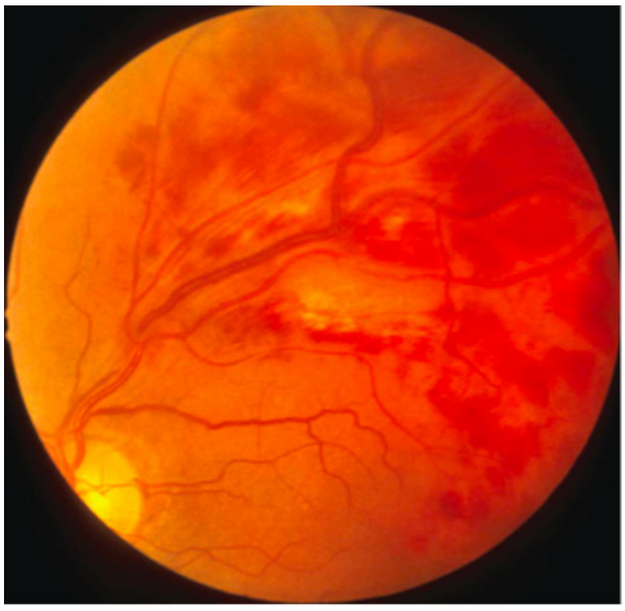

Figure 1: Major BRVO

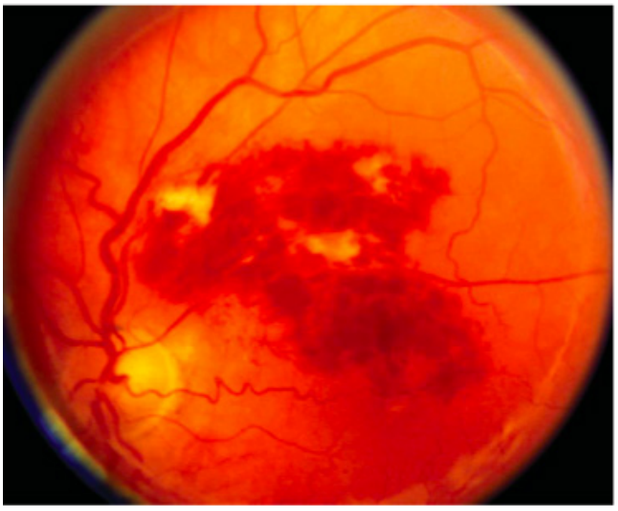

Figure 2: Macular BRVO

Visual fields: Initially in the region of the temporal BRVO, minimal to mild defect was seen in 72% and moderate in 26%. On follow-up, in temporal BRVO, visual field defect improved or remained stable in 68% of eyes with minimal-mild initial defect, and improved in 52% of eyes with moderate to severe initial defect[6].

Management options

Central lasers in BRVO: For many years central laser was the treatment modality of choice following the results of the Branch Vein Occlusion Study (BVOS)[8]. It reported spontaneous improvement in about one-third of cases in the first 3 months. Grid laser was performed at 3 months in eyes that had persistent ME or VA less than 20/40.

At the end of 3 years, treated eyes were more likely to gain 2 lines of visual acuity (65%) compared to untreated eyes (37%). Furthermore, treated eyes were more likely to have 20/40 or better vision at 3 years follow-up (60% vs 34% untreated), with a mean visual acuity improvement of 1.3 lines ETDRS versus 0.2 lines in the untreated group[8].

Intravitreal steroids: The gains from laser as can be seen were not startling. Intravitreal steroids in the form intravitreal triamcinolone (IVTA, 1mg and 4mg) were then tested against laser in the Standard Care vs. Corticosteroid for Retinal Vein Occlusion (SCORE) trial[9]. There was no significant difference in terms of visual acuity of central foveal thickness at 1 year. There were however significant number of cases of cataract and raised IOP in the 4mg IVTA group.

A sustained release form of dexamethasone, Ozurdex was tested the GENEVA Study[10]. Peak visual acuity improvement was seen at day 60 with deterioration of vision after 3 months. A repeat injection at 6 months yielded similar results.

AntiVEGF drugs

Ranibizumab: Elevated levels of VEGF have been found in BRVO hence the rationale to treat macular oedema

in BRVO with antiVEGF drugs. Campochiaro *et al*[2] established through a clinical trial that run over 2 years that visual acuity and anatomical gains were far greater in the ranibizimuab group (both 0.3mg and 0.5mg) than in the sham group. They started off with 6 monthly injections then switched to PRN dosing. Most patients required 0-3 injections in the 2nd year showing that there is need for several injections to maximize patient benefit and that long-term follow up is important.

Bevacizumab: Bevacizumab has been found to be effective with both Pro Re Nata (PRN) dosing and Treat and extent (TREX) dosing. In the PRN regimen, re-injection was done if the foveal thickness was >250 or there was persistent or recurrent macular edema affecting visual acuity. Patients required 3.8 ± 1.5 injections over 2 years with a provision for rescue laser at the end of 3 months[11].

TREX dosing was also found to be as effective, however it was found to require fewer injections over time which could translate to significant cost savings[12]. A comparison between ranibizuman and bevacizumab was carried out in the MARVEL study with each drug administered on a PRN basis for the management of BRVO with macular edema. Both drugs resulted in a rapid restoration of anatomy and function with a mean increase in visual acuity (ranibizumab-18.08 letters and bevacizumab-15.55 letters). Rescue laser therapy was only needed in 16% of eyes[13].

A comparison of the efficacy of bevacizumab to grid laser reported that bevacizumab treatment resulted in better and faster visual recovery[14]. Commencing treatment early with AntiVEGF agents has also been shown to have maximum visual benefit. The vision gained in eyes treated with anti-VEGF agents from the beginning was 18.3 letters at the end of 12 months compared to 12.1 letters when the patient was initially treated with sham and crossed over to anti-VEGF agents at the end of 6 months *(P* < 0.01)[15].

Aflibercept: Aflibercept is one of the latest additions to the AntiVEGF family of drugs. It is a soluble receptor fusion protein with a VEGF binding affinity and duration of action in the eye greater than its predecessors. It also binds to other angiogenic factors including placental growth factors.

The VIBRANT study was a double-masked, multicenter trial to assess the efficacy of aflibercept compared to macular laser in eyes with macular edema secondary to BRVO. Patients in one arm of the study received 6 injections of 2 mg aflibercept, and patients in the other arm received baseline laser. Rescue laser therapy occurred as needed after 12 weeks. At the end of 6 months, the eyes treated with aflibercept had more favorable outcomes in terms of reduced central foveal thickness (aflibercept 280.5 microns/laser 128microns) or visual recovery (aflibercepept 17 letters/laser 6.9 letters)[16]. Outcomes at 52 weeks follow-up indicated that aflibercept injections at 8 weeks interval after the first 6 months helped maintain vision and foveal thickness in the aflibercept arm of the study[17].

Medical therapy

It is reported that an increase in small platelet aggregates may play a component in BRVO pathogenesis.

Houtsmuller *et al*[18] compared the effect of ticlopidine, an antiplatelet aggregative factor, versus placebo in 54 patients with BRVO and found a significant improvement in visual acuity in 69% BRVO patients of ticlopidine group versus 52% of the placebo group in a six-month follow-up.

Glacet Bernard *et al*[19] examined the efficacy of troxerutin, an antierythrocyte and antiplatelet aggregative drug, versus placebo in 26 patients with BRVO less than five months from symptom onset. In a two-year follow-up, there was a significant improvement in visual acuity, as well as in macular edema, in patients treated with troxerutin compared to those treated with placebo.

Tissue Plasminogen Activator (t-PA) intravitreally or directly into the retinal vein is another treatment option for BRVO. Small studies have demonstrated safety and an improvement in visual acuity and foveal thickness with t-PA treatment[20,21].

Low-Molecular-Weight Heparins (LMWHs) have also been used and are considered to be effective for the treatment of BRVO with improved visual acuity, supporting the hypothesis that BRVO is a venous thrombotic disorder. No increased risk of vitreous haemorrhages was observed during treatment with LMWH[22,23].

Combination therapy

Tomomatsu *et al*[24] assessed the efficacy of bevacizumab combined with Targeted Retinal Photocoagulation (TRP) compared to bevacizumab alone and concluded that the combination therapy helped reduce recurrence of macular edema.

The RELATE trial evaluated the combination of grid and scatter photocoagulation 24 weeks after randomization into the ranibizumab group. The authors found no additional benefits of laser in terms of improvement in vision, resolution of macular edema, or reduced number of intravitreal injections[25].

The Retinal Vein Occlusion Associated Macular Edema study (RABAMES) compared the efficacy of intravitreal ranibizumab to grid laser and combination therapy. In this study, treatment was instituted immediately and duration of follow-up was 6 months. The eyes in the ranibizumab group were treated with 3 monthly injections followed by observation for the next 3 months. The study found that eyes treated with ranibizumab recovered vision faster than the grid laser and the combination group. There was no distinct advantage of combination therapy over ranibizumab in terms of functional or vision recovery or prevention of recurrence. However, foveal thickness increased in the ranibizumab group whereas it decreased in the grid laser group between months 3 and 6 follow-ups with no associated variation in visual acuity[26].

Azad *et al*[27] compared the efficacy of ranibizumab and laser, bevacizumab and laser with that of laser alone in the management of BRVO with macular edema. The authors found that the gain in visual acuity in the ranibizumab-laser group was significantly higher than the bevacizumab-laser group or the laser-only group. The bevacizumab-laser group also had better gains in visual acuity compared to the laser only group. There was no significant difference in the reduction of CFT in each of the three groups. The authors concluded that a combination of anti-VEGF agents and early laser results in better gains in visual acuity and reduces the number of subsequent injections.

A Cochrane database review reported that there is no benefit in performing early (before 3 months) or late laser (after 6 months) in eyes with macular edema secondary to BRVO[28].

The European Vitreoretinal Society (EVRS) also found that for medical management, monotherapy with anti-VEGF agents were superior to any form of combination therapy[29].

Surgical management

Parsplana vitrectomy with ILM peeling is being suggested as an option for the management of macular edema with BRVO. The rationale for this treatment includes relief of traction, improved oxygenation of vitreous and retina thereby preventing photoreceptor loss, removal of inflammatory, and permeability factors such as VEGF and upregulation of epidermal growth factors which help the healing process. The EVRS found vitrectomy with ILM peeling was the most effective management reporting visual gains that were almost twice as high as anti-VEGF agents at 24 months postoperatively[29].

Scatter laser: Scatter laser to the affected quadrant is part of the care given by some ophthalmologists. This helps reduce the VEGF drive by ablating ischaemic retina. It has been shown to be effective in the management of ME secondary to BRVO when used in combination intravitreal avastin and macula grid laser with a reduction in CMT and improvement in VA[30].

Looking ahead: Conbercent is a novel antiVEGF agent. It is a recombinant fusion protein of key extracellular domains from human VEGF receptors 1 and 2 and IgG Fc produced in a Chinese hamster ovarian cell line. It blocks all VEGF-A isoforms as well as VEGF-B, VEGF-C, and placental growth factor. Intravitreal injection of conbercept is shown to be safe and effective for the treatment of ME secondary to BRVO, based on 6-month follow-up data with no significant differences in terms of reduction in central macular thickness, visual acuity improvement and average number of injections compared to ranibizumab[31].

Ziv-aflibercept (Zaltrap; Regeneron, New York, USA), is an antiVEGF drug which is a recombinant fusion protein with a similar mechanism to aflibercept. It has been shown in a case report by Chhablani[32] to be effective in the management of macular oedema secondary to CRVO. Studies on its effect in macular oedema secondary to BRVO are still pending.

Subthreshold grid laser therapy has been studied for its effects on macular oedema secondary to BRVO and it was found to be as effective as standard threshold grid laser in terms of reduced foveal thickness and visual acuity gains at 6 months, 1 year and 2 years[33].

Subthreshold laser has also been found to be useful in reducing central macular thickness in patients with persistent macular oedema secondary to BRVO without inducing any significant retinal damage especially in cases where the vision was >20/40[34].

CONCLUSION

Branch retinal vein occlusion is the second most common retinal vascular disease after diabetic retinopathy and can be a potentially blinding condition. Since the BVOS, there are now several modalities of treatment that can be employed ranging from threshold and subthreshold lasers, intravitreal corticosteroids and antiVEGF agents as well as systemic agents. These have all been shown to stabilize, hasten recovery and/or improve visual acuity while at the same time alleviating complications such as neovascular glaucoma and vitreous haemorrhage.

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